

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-422 / S-032

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-422/S-032

Xttrium Laboratories, Inc.
Attention: Ram Chakroborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, IL 60609-2731

Dear Dr. Chakroborty:

Please refer to your supplemental new drug application dated January 10, 2002, received February 25, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 2% chlorhexidine gluconate solution.

We acknowledge receipt of your submissions dated August 22, September 3, and October 22, 2003.

Your August 22, 2003, submission constituted a complete response to our August 11, 2003, action letter.

This supplemental new drug application provides for revised labeling and directions for use for a pre-operative skin preparation.

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must submit draft labeling revised as follows:

1. Add the phrase "Peel here for **Drug Facts**>" to the outermost surface of the 4- and 8-ounce containers, rather than on page 2 of the leaflet. The statement is located on the wrong panel. Currently, the statement appears *inside* the folded label, but should be located on the principal display panel (PDP) so that it is visible to the reader looking at the bottle.

In addition, all previous revisions as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

You are encouraged to contact the Division of Over-the-Counter Drug Products regarding the content and format of your safety update [under 21 CFR 314.50(d)(5)(vi)(b)] prior to responding to these deficiencies.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 19-422/S-032

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If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.

Director

Division of Over-the-Counter Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

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/s/

Charles Ganley
10/27/03 04:27:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-422/S-032

Xttrium Laboratories, Inc.
Attention: Ram Chakroborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, ILL 60609-2731

Dear Dr. Chakroborty:

Please refer to your supplemental new drug application dated January 10, 2002, received February 25, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dyna-Hex 2 (chlorhexidine gluconate 2%) Solution.

We acknowledge receipt of your submissions dated February 10 and March 26, 2003.

Your submission of February 10, 2003, constituted a complete response to our December 19, 2002, action letter.

This supplemental new drug application provides for revised labeling and directions for use for a pre-operative skin preparation.

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

We have reviewed the information you provided to support the position that you should not be required to list the inactive ingredients in the labeling of your products that contain chlorhexidine gluconate. We have also obtained additional information from the agency's inspection of your company conducted from May 12, 2003 to June 23, 2003. This letter constitutes our tentative denial of your request.

A. Federal Food, Drug, and Cosmetic Act (FFDCA)

You state that Section 502(e)(1)(A)(iii) of the FFDCA [21 USC 352(e)(1)(A)(iii)], enacted as part of the Food and Drug Modernization Act of 1997, includes a provision that a drug is misbranded unless its label bears the established name of each inactive ingredient, *except that nothing in the subsection requires that any trade secret be divulged* [emphasis added].

We concur that the FFDCA contains this provision.

B. 21 CFR 720.8

We referred you to 21 CFR 720.8, which discusses the content of a request for confidentiality of the identity of ingredients and lists six factors that the FDA will consider in determining whether the identity of an ingredient qualifies as a trade secret. You address these six factors in your letter of February 10, 2003.

(1) THE EXTENT TO WHICH THE IDENTITY OF THE INGREDIENT IS KNOWN OUTSIDE PETITIONER'S BUSINESS

You state that, _____

We are not contesting your statements regarding this factor at this time.

(2) THE EXTENT TO WHICH THE IDENTITY OF THE INGREDIENT IS KNOWN BY EMPLOYEES AND OTHERS INVOLVED IN PETITIONER'S BUSINESS

You state that the formulas for your chlorhexidine gluconate products are _____

We are not contesting your statements regarding this factor at this time.

(3) THE EXTENT OF MEASURES TAKEN BY THE PETITIONER TO GUARD THE SECRECY OF THE INFORMATION

You restate the information under number (2) above. You add that you have _____

We are not contesting your statements regarding this factor at this time.

(4) THE VALUE OF THE INFORMATION ABOUT THE IDENTITY OF THE CLAIMED TRADE SECRET INGREDIENT TO THE PETITIONER AND TO ITS COMPETITORS

You state that _____% of your business is the manufacture and sale of your chlorhexidine gluconate products and that you produce over _____ of all such products used in the United States. You add that these products are not only safe and effective, but also gentle to the skin, and that your formulations are widely accepted by health care personnel. You attribute these factors as primary reasons for your success in marketing these products. You contend that disclosure of the inactive ingredients in your products would provide your competitors with confidential information that would allow them to bypass the lengthy and costly research and development process in creating competitive chlorhexidine gluconate products, which you describe as a complex undertaking. You describe a

number of these complexities involving inorganic anions, surfactants, alcohol, and pH of the final product to develop a stable and non-irritating product. You conclude that disclosure of the inactive ingredients in your products would have a significant impact on your business.

We note your comments that your product is "gentle to the skin" and "widely accepted by health care personnel." You attribute these factors as primary reasons for your success in marketing these products and use this argument to support the value to you of nondisclosure of the inactive ingredients in these products.

We also note your correspondence to FDA dated October 8, 2002 and April 9, 2003 stating that, as of those dates, there have been no reports of any adverse effects received at your company regarding 2% chlorhexidine gluconate (NDA 19-422). As you are aware, during the recent FDA inspection of your company, our inspectors found several adverse reaction reports for the chlorhexidine gluconate products marketed under this NDA that were not reported to FDA: complaints [your numbers] 000214 (skin rashes in 4 people) and 990602-A (severe skin reactions in 3 hospital staff members). Our inspectors also found a number of adverse reaction reports for your chlorhexidine gluconate products marketed under other NDAs that were not reported to FDA. These reports cast considerable doubt on the value of the identity of the ingredients you wish to shield. If such ingredients do not in fact mitigate irritation, then the marketing success of the product cannot be attributed to its supposed gentleness to the skin.

Further, the _____ obtained in our inspection _____ and are therefore not adequate to serve as an adverse reaction reporting system. Our inspection also revealed that your company did not have standard operating procedures in place for collecting, evaluating, processing, and submitting adverse event reports to FDA [in violation of 21 CFR 314.80]. It is impossible to determine how many adverse reactions to your product have actually occurred because of your noncompliant system for collecting and evaluating adverse event reports. Without such a system in place, there is no procedure to collect and save all adverse event reports and, therefore, the existence of only a limited number of reports fails to demonstrate the value of your inactive ingredients in alleviating irritation, as you contend.

(5) THE AMOUNT OF EFFORT OR MONEY EXPENDED BY PETITIONER IN DEVELOPING THE INGREDIENT

You state that your formulas were developed by chemists who initially prepared and tested _____ different formulations and that the initial testing was done to determine the products' cosmetic qualities (gentle to the hands). You add that it took _____ to develop your formulas and cost over _____ dollars.

We are not contesting your statements regarding this factor at this time.

(6) THE EASE OR DIFFICULTY WITH WHICH THE IDENTITY OF THE INGREDIENT COULD BE PROPERLY ACQUIRED OR DUPLICATED BY OTHERS

You state that you do not believe that it is possible to duplicate formulas without undergoing the same extensive procedures and processes that you undertook to develop your formulas. You contend this would take many years of research and development at great expense to anyone seeking to duplicate your formulas. You conclude by stating that you have undertaken extreme measures to maintain the

secrecy of your formulas and it is not possible to acquire them without undertaking extensive research and development procedures.

We have reviewed your product formulation for Exidine (NDA 19-422) and the product formulation for a competing product, Cidastat (NDA 19-258). Both products contain chlorhexidine gluconate. We note that these two products have a number of common inactive ingredients. See chart below.

| Exidine (NDA 19-422) | Cidastat (NDA 19-258) |
|------------------------------|-----------------------|
| ———— (hydroxyethylcellulose) | Hydroxyethylcellulose |
| ———— (lauramine oxide) | Lauramine oxide |
| ———— (cocamide DEA) | Cocamide DEA |
| Isopropyl alcohol | Isopropyl alcohol |
| Purified water | Purified water |

There is a slight difference in the remaining inactive ingredients present in the products. Your Exidine product contains citric acid, while the Cidastat product contains several other ingredients. The presence of alcohol is listed in each product's labeling. While we cannot disclose the percentage of the inactive ingredients in each product, it appears that others can accomplish qualitative duplication of the Exidine formulation.

Both products were approved at about the same time. Your NDA was approved on December 17, 1985, and the Cidastat NDA was approved on July 22, 1986. Further, the NDA for Cidastat was submitted in April 1984 before the NDA for Exidine was submitted in January 1985. Based on the time that product testing necessarily would have been conducted under an IND, the time that the NDA for each product was submitted, and the requirements with respect to formulation that must be satisfied before an NDA can be filed, at least one other company was able to develop a similar product formulation even before your product was approved for marketing. This could indicate that the inactive ingredients used in both products were easily obtained and logical inactive ingredients to use in these types of product formulations. It might also indicate that it was not necessary to wait until your product was approved for marketing to conduct "reverse engineering" to determine the inactive ingredients present in your product formulations.

We have also looked at the formulation of other approved chlorhexidine gluconate products. Several contain ————— or N,N-diethyl lauramine oxide. Again, this appears to indicate that these ingredients are common inactive ingredients to use in these types of product formulations.

C. Other Reasons to List the Inactive Ingredients in Product Labeling

FDA's Adverse Events Reporting System (AERS) contains over 2,500 reports of adverse events associated with products containing chlorhexidine gluconate as of April 2003. The majority of these reports involved products containing 4% chlorhexidine gluconate. The greater number of reports for products containing 4% (compared to products containing 2% or less) is likely the result of the higher concentration of the active ingredient itself, which is known to be a dermal irritant. We cannot determine whether fewer reports for products with lower concentrations results from the inactive ingredients in the products.

As noted above, your company did not have a system in place for collecting, evaluating, processing, and submitting adverse event reports to FDA [in violation of 21 CFR 314.80]. Without such a system,

we conclude that it is not possible to determine (1) if your formulation is less likely to be irritating, as you contend, or (2) the value of the inactive ingredients in your products in decreasing adverse events.

We also have concerns about your products possibly being misbranded under sections 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act because they do not identify all of the inactive ingredients in the products. We note that the labeling for your products contains the following statements under the Warnings section: "Do not use if you are allergic to chlorhexidine gluconate or any other ingredients ***." "Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition." The inactive ingredients are listed as "4% isopropyl alcohol in a nonalkaline base."

FDA has stated on many occasions that it considers the inclusion of inactive ingredients in product labeling beneficial to consumers and health professionals in helping to determine the cause of adverse reactions. This applies to the listing of all inactive ingredients in all of your chlorhexidine gluconate products.

Without full disclosure of all of the inactive ingredients, users of these products are unable to follow your warning to determine if they are allergic to any other ingredients because all of those ingredients are not identified. Thus, your product labeling may be misleading [section 502(a)] and fail to bear adequate warnings against unsafe use [section 502(f)].

D. Conclusion

We have determined that the information you have provided does not support two of the six factors that we consider to determine whether the identity of an ingredient qualifies as a trade secret. These are factors number 4 and 6 discussed above. Accordingly, we tentatively conclude that you should be required to list the inactive ingredients in the labeling of all of your OTC drug products that contain chlorhexidine gluconate to meet the requirements of section 502(e)(1)(A)(iii) of the FFDCA.

Pursuant to 21 C.F.R. § 720.8(e), you may either withdraw the records for which we have tentatively denied your request for confidentiality or submit within 60 days from the date of receipt of this notice additional relevant information and arguments and request that the agency reconsider its decision in light of both the original material and the information that was originally submitted.

In addition, you must submit draft labeling revised as follows. Refer to the attached prototype Principle Display Panels (PDPs) for more information.

1. Place the established drug name (chlorhexidine gluconate 2% solution) in direct conjunction with the trade name, followed by the pharmacological category (antiseptic).
2. Revise the 16- and 30-ounce and 1-gallon container labels to retain the standard order and required flow of *Drug Facts* information onto multiple panels, as required by 21 CFR 201.66(d)(5). Relocate Net Contents, Lot Number and Expiration Date information so as not to interrupt the flow and order of the *Drug Facts* panels.
3. Revise the PDPs for the 30- and 32-ounce container sizes so that the net contents information is listed only once, and is contained in the lower 30% of the PDP. Refer to 21 CFR 201.62(e) for clarification.

4. Revise the *Drug Facts* labeling for all container sizes to incorporate barlines that surround information by a box or similar enclosure, as required by CFR 201.66(d)(8).
5. Revise the 4- and 8-ounce container labels so that their outermost labeling surfaces contain the title, headings, subheadings and information set forth in paragraphs (c)(1) through (c)(8) in 21 CFR 201.66. Adding the phrase "Peel here for Drug Facts→" to the outermost surface of your 4 and 8 ounce container labeling would satisfy this requirement. Refer to 21 CFR 201.66(c) for further information.
6. Revise the laminate panels for the 4- and 8-ounce containers to include the statement "*Drug Facts* (continued)" directly above the header **Directions** on the next adjacent panel.
7. Revise the labeling for the 16-, 30-, 32-ounce, and 1-gallon container sizes so that the bulleted statements under *Directions* are vertically aligned, to ensure visual separation and adequate white space between discrete chunks of information. Bulleted statements can be only wrapped when using the modified format. See 21 CFR 201.66(d)(10).
8. Remove "—————" from the 8-ounce container labels currently located after *Active ingredient*; at the end of the bulleted statement **patient preoperative skin preparation**, under *Uses*; after **Do not use**; and, at the end of the first bulleted statement under **When using this product**.

In addition, we encourage the following revisions to your proposed labeling. The following revisions are not required for approval.

9. Under *Questions or comments?*, for the 16-ounce container size, revise your labeling to include a telephone number for consumer inquiries. Specify the days of the week and the hours of operation when a person is available to respond to questions.
10. Revise the labeling for the 4- and 8-ounce containers so that the *Drug Facts* contents fit within the two panels inside the leaflet. Thus, place the first panel (page 2) directly behind the PDP, and the second panel (page 3) flush against the container so that it is immediately visible. The exposed *Drug Facts* panel should include the *Directions*, *Other information*, *Inactive ingredient*, and *Questions?* sections.
11. Left justify *Active ingredient* information and right justify the corresponding *Purposes* information so that it runs continuously, on one line for the 4- and 8-ounce container labels.
12. Under *Active ingredient*, place the phrase "chlorhexidine gluconate 2% solution" on two separate lines, so that the phrase "chlorhexidine gluconate" lies on the first line, and "2% solution" lies on the second line followed by a succession of dots for the 4- and 8-ounce container labels.
13. Remove the term "—————" that follows the **Warnings** and **Directions** headers for the 4- and 8-ounce container labels, to reduce redundancy and confusion with required "*Drug Facts* (continued)" headers.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

NDA 19-422

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Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

PROTOTYPE : 4 ounce container label
 (Also used this prototype for 8 ounce container label.)

Page 2

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| Drug Facts | |
|---|---|
| Active ingredient chlorhexidine gluconate 2% solution..... | Purposes surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing |
| Uses | |
| <ul style="list-style-type: none"> • surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care • healthcare personnel handwash: helps reduce bacteria that potentially can cause disease • patient preoperative skin preparation: preparation of the patient's skin prior to surgery • skin wound and general skin cleansing | |
| Warnings | |
| For external use only | |
| Do not use • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face | |

| Drug Facts (continued) |
|---|
| When using this product |
| <ul style="list-style-type: none"> • keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums • if solution should contact these areas, rinse out promptly and thoroughly with water • wounds which involve more than the superficial layers of the skin — not be routinely treated • repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin |
| Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition. |
| Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away. |

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Page 1

| | |
|---|-----------------------------------|
| | <i>Peel here for Drug Facts</i> ➔ |
| | NDC 17187-1021-2 |
| DYNA-HEX2[®] (Chlorhexidine Gluconate 2% Solution) Antiseptic | |
| Contains: 2% Chlorhexidine Gluconate Manufactured By: Xtrium Laboratories, Inc. 415 West Pershing Road Chicago, IL 60609 | |
| FOR EXTERNAL USE ONLY | |
| Net Contents: | 4 fl oz (118 mL) |
| Lot Number: | |
| Exp. Date: | |

PROTOTYPE : 4 ounce container label

(Also used this prototype for 8 ounce container label.)

| | | | |
|--|--|----------------------|--|
| Drug Facts (continued) | | | |
| Directions | | | |
| <p>Surgical hand scrub: • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush, paying close attention to the nails, cuticles, and skin between the fingers</p> <p>• rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • dry thoroughly</p> <p>Healthcare personnel handwash: • wet hands with water • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • rinse and dry thoroughly</p> <p>Patient preoperative skin preparation: • apply product liberally to surgical site and swab for at least 2 minutes • dry with a sterile towel</p> <p>• repeat procedure for an additional 2 minutes and dry with a sterile towel</p> <p>Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly</p> | | Laminate Flap | |
| Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F) | | | |
| Inactive ingredients _____ | | | |
| Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM | | | |
| | | | |

**APPEARS THIS WAY
ON ORIGINAL**

PROTOTYPE: 16 ounce container label
(Also use this prototype for 1 gallon container label.)

NDC 17187-1021-3

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xttrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609

FOR EXTERNAL USE ONLY

Lot Number:
Exp. Date:

Net Contents: 16 fl oz (1 pt) (473 mL)

| Drug Facts | |
|--|---|
| Active ingredient chlorhexidine gluconate 2% solution..... | Purposes surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing |
| Uses <ul style="list-style-type: none">• surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care• healthcare personnel handwash: helps reduce bacteria that potentially can cause disease• patient preoperative skin preparation: preparation of the patient's skin prior to surgery• skin wound and general skin cleansing | |

PROTOTYPE: 16 ounce container label continued.

(Also use this prototype for 1 gallon container label.)

| |
|--|
| Drug Facts (continued) |
| Warnings For external use only |
| Do not use • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face |
| When using this product • keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums • if solution should contact these areas, rinse out promptly and thoroughly with water • wounds which involve more than the superficial layers of the skin _____ not be routinely treated • repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin |
| Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition. |
| Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away. |
| Directions Surgical hand scrub: • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush, paying close attention to the nails, cuticles, and skin between the fingers • rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • dry thoroughly Healthcare personnel handwash: • wet hands with water • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • rinse and dry thoroughly Patient preoperative skin preparation: • apply product liberally to surgical site and swab for at least 2 minutes • dry with a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly |
| Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F) |
| Inactive ingredients |
| Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM |

PROTOTYPE: 30 ounce container label
(Also use this prototype for 32 ounce container label.)

NDC 0116-4242-30

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

| | |
|------------------|---|
| Contains: | 2% Chlorhexidine Gluconate |
| Manufactured By: | Xttrium Laboratories, Inc. 415 West Pershing Road Chicago, IL 60609 |

FOR EXTERNAL USE ONLY

30 fl oz (887 mL)

Lot Number:
Exp. Date:

PROTOTYPE: 30 ounce container label continued.
 (Also use this prototype for 32 ounce container label.)

| Drug Facts | |
|---|---|
| Active ingredient chlorhexidine gluconate 2% solution..... | Purposes surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing |
| Uses | |
| <ul style="list-style-type: none"> • surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care • healthcare personnel handwash: helps reduce bacteria that potentially can cause disease • patient preoperative skin preparation: preparation of the patient's skin prior to surgery • skin wound and general skin cleansing | |
| Warnings | |
| For external use only | |
| <p>Do not use</p> <ul style="list-style-type: none"> • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face | |
| When using this product | |
| <ul style="list-style-type: none"> • keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums • if solution should contact these areas, rinse out promptly and thoroughly with water • wounds which involve more than the superficial layers of the skin — not be routinely treated • repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin | |
| <p>Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition. Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.</p> | |
| Directions | |
| <p>Surgical hand scrub:</p> <ul style="list-style-type: none"> • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers • rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • rinse and dry thoroughly <p>Healthcare personnel handwash:</p> <ul style="list-style-type: none"> • wet hands with water • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • dry thoroughly <p>Patient preoperative skin preparation:</p> <ul style="list-style-type: none"> • apply product liberally to surgical site and swab for at least 2 minutes • dry with a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel <p>Skin wound and general skin cleansing:</p> <ul style="list-style-type: none"> • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly | |
| Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F) | |
| Inactive ingredients | |
| Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM | |

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/s/

Charles Ganley
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-422/S-032

Xttrium Laboratories, Inc.
Attention: Ram Chakroborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, IL 60609-2731

Dear Dr. Chakroborty:

Please refer to your supplemental new drug application (NDA) dated January 10, 2002, received February 25, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exidine (2% chlorhexidine gluconate) solution.

We also refer to your amendments dated March 4, June 20, July 2 and 18, August 7, 12, 15, and 30, September 12 and 24, October 7, and November 6, 2002.

This supplemental new drug application provides for revised **Directions for Use** for the pre-surgical scrubbing indication.

We completed our review of this application, as amended, and it is approvable.

In order for this supplement to be approved, it will be necessary for you to address the following deficiencies in your proposed labeling.

1. We have considered your contention that the inactive ingredients for Exidine Solution 2% and Dyna-Hex 2% products need not be listed in the labeling for these products in accordance with Section 502(e)(1)(A)(iii) of the Federal Food, Drug, and Cosmetic Act because you consider that information to be a trade secret. We have determined that we need additional information related to this issue before we can decide on appropriate labeling.

We refer you to 21 CFR 720.8, which sets forth the information that an applicant must provide to the agency in connection with a request for confidentiality of the identity of ingredients, as well as listing six factors FDA will consider in determining whether or not the identity of an ingredient qualifies as a trade secret. Although this regulation applies to cosmetic products, we find the information and six factors equally applicable to determining whether inactive ingredients in an OTC drug product qualify as a trade secret. Accordingly, we request that you provide the information listed in 21 CFR 720.8, including information relating to the six factors therein, for each inactive ingredient in the Exidine Solution 2% and Dyna-Hex 2% products for which you claim trade secret status. In addition, we also invite you to submit any other information that you believe supports your contention that the ingredient(s) is/are trade secret(s).

2. Principal Display Panel (PDP)

Refer to the PDP prototype in Attachment 1 for guidance in making revisions to your labeling.

- a. Revise the established name and the pharmacologic category on all labels to be in bold print, in accordance with 21 CFR 201.61(c).
 - b. Revise all labeling so that the established name directly follows the pharmacologic category, and both statements are positioned in direct conjunction with the most prominent display of the trade name, in accordance with 21 CFR 201.61.
 - c. Revise the PDP for the 32 ounce and 1 gallon containers so that the same size font is used to list both the established name of the drug and the pharmacologic category, in accordance with 21 CFR 201.61.
 - d. Enlarge the font size for the statements of identity included in the labeling for the 4 and 8 ounce containers in order to increase their prominence.
 - e. Revise all labels to have the net contents in the lower 30 percent of the PDP, as required by 21 CFR 201.62.
3. The following deficiencies refer to your proposed **Drug Facts Labeling (DFL)**:

A marked up Drug Facts Labeling (DFL) prototype is attached for your reference in making the labeling revisions required for this supplement (Attachment 2). This DFL prototype includes labeling revisions that must be made for *all* your products and container sizes. The strike-through feature highlights sections of your labeling that must be deleted. Additional language that is required in the text of your labeling appears in shaded text in the appropriate sections of your DFL.

In addition to the revisions included in the marked-up DFL prototype, you must make the following specific revisions in order for the labeling for this supplement to be approved:

- a. In order to improve the legibility of your labeling, verify that the labeling for the 4 and 8 ounce containers comply with the leading (space between two lines) requirements, as described in 21 CFR 201.66(d)(3).
- b. Revise the bulleted statements under the directions for use as a surgical handscrub to comply with 21 CFR 201.66(d)(4), or justify your use of a modified format for the 16 ounce label. (Refer to marked-up DFL prototype, attached.)
- c. Realign the bulleted statements under the *Directions* section for surgical handscrubs in order to comply with 21 CFR 201.66(d)(4).
- d. Revise the bulleted statements under the *Directions* section for patient preoperative skin preparations and surgical hand scrubs, and under the *Do not use* section for the 32 ounce label, in order to comply with 21 CFR 201.66(d)(4).

- e. Remove the phrase “ _____ ” from the bottom of the first labeling panels for the 16 ounce and 1 gallon labels.
 - f. Increase the font size in the Inactive ingredients section of the labeling for the 4 and 8 ounce sizes, so that all your *Drug Facts* headings are the same size.
 - g. Under *Directions*, correct the spelling of the subheading “ _____ personnel handwash” so that it reads “Healthcare personnel handwash” (1 gallon container size).
 - h. Identify the location of the lot number and expiration date on each package.
4. In addition to the above comments, the following comments apply specifically to the 30 ounce labeling for “Allegiance” proposed in this supplement.
- a. Widen the space between each line (leading) of text in your labeling so that it is at least 0.5-point and conforms to the requirements described in 21 CFR 201.66(d)(3).
 - b. Ensure that the bullets beside each bulleted statement are at least 0.5 point.
 - c. Bulleted first statements under *Warnings* subheadings titled, “When using this product”, “Directions” for “Surgical Hand Scrub” and “Skin wound and general skin cleansing” need to be vertically aligned with the other bulleted statements.
 - d. Under the “Do Not Use” subheading under *Warnings*, correct the spelling of the word “ _____ ” to read “meninges”.
 - e. Increase the font size in the *Questions or Comments* heading so that it is identical to the font size of the other headings.

To facilitate review of your submission, provide a highlighted or marked-up copy of any revised labeling incorporating the revisions requested in this letter. In addition, all previous revisions, as reflected in the most recently approved labeling, must be included.

If additional information relating to the safety or effectiveness of this drug becomes available, you may need to make further revisions to your labeling.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b) and in the following section of this letter. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

- Describe in detail any significant changes or findings in the safety profile.
- When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - ◆ Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - ◆ Present tabulations of the new safety data combined with the original NDA data.
 - ◆ Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - ◆ For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
- Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
- Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

Charles Ganley, MD
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosures: 1) Principal Display Panel Prototype
2) Drug Facts Labeling Prototype

5 page(s) of draft
labeling has been
removed from this
portion of the ~~review~~.

LETTER

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
12/19/02 11:46:51 AM